REMARKS

The phrase "stationary phase" in the claims has been amended to recite "dormant". The phrase "stationary phase" meaning "dormant" is discussed in relation to *Mycobacterium tuberculosis, inter alia*, on page 2, line 23 to page 3, line 3 of the present specification, i.e., not actively growing bacteria. Hence, the amendments to the claims do not constitute new matter, and thus entry is requested.

On page 2 of the Office Action, the Examiner notes a typographical error in Claim 9 (iii) in the recitation of "said test compound said test compound".

Applicants hereby amend Claim 9 to correct this obvious typographical error.

In addition, on page 2 of the Office Action, the Examiner rejects Claims 2-7 and 9-10 under 35 U.S.C. §112, second paragraph.

Specifically, the Examiner states that in Claims 4, 6, 7 and 9, the expression "strain" is indefinite. The Examiner suggests amending Claim 4 to recite "said bacterial strain is selected from a strain in the group consisting of the species...".

Applicants hereby amend Claim 4 as suggested by the Examiner. Further, Applicants hereby amend Claims 6 and 7 in a manner consistent with the amendments to Claim 4.

In addition, the Examiner states that Claim 9 is confusing in that such is directed to a method of "identifying whether the test compound has any bacterial activity", while the steps include using a composition having unidentified ingredients

comprising the "test compound"; and Claim 9 further is drawn to an optional isolation step of the test compound from the composition. The Examiner states that the claim is unclear since the origin and nature of the test compound is not disclosed.

In view of the amendments to Claim 9 to delete reference to the composition and the isolation step, Applicants respectfully submit that the Examiner's rejection has been rendered moot.

The Examiner also states that Claim 9 is indefinite in view of the expression "antibacterial activity against stationary phase bacteria" since antibacterial activity is dose dependent and most compounds have at least some antibacterial activity if used at high enough concentrations.

The Examiner notes Applicants' argument that the concentration of antibiotic employed will depend upon the bacterial strain employed and can be readily determined by one skilled in the art. However, the Examiner contends that this involves testing a myriad of diverse bacterial strains with a myriad of diverse antibiotics.

However, the fact that testing may be required is not the standard for whether the claims lack enablement, i.e., whether or not there is undue experimentation. That is, if the experimentation (testing) is routine, even though it may be extensive, it still is not undue experimentation. Applicants respectfully submit that only routine experimentation is required to determine the appropriate antibiotic concentration. Thus, the Examiner's rejection is legally improper.

More specifically, the method of testing multiple concentrations of antibiotic is no different to the common method of measuring the normal minimum inhibitory concentration (MIC). Persons skilled in the field of bacteriology and antibacterial agents use this testing procedure as part of their day to day clinical and/or laboratory work. Hence, the measurement of suitable concentrations of multiple antibiotics poses no more an onerous burden of experimentation on the skilled person than they would undertake in their day to day activities.

Accordingly, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and are enabled by the present specification. Thus, Applicants request withdrawal of the Examiner's rejection.

On page 4 of the Office Action, the Examiner maintains the rejection of Claims 3-4, 6-7 and 9-10 under 35 U.S.C. §103 as being unpatentable over Sahm et al taken in view of Pelczar et al, George et al, Shomura et al and Barth for the reasons of record.

In addition, on page 5 of the Office Action, the Examiner maintains the rejection of Claim 5 under 35 U.S.C. §103 as being unpatentable over Sahm et al taken in view of Pelczar et al, Shomura et al or Barth, and in further view of Murray et al and *The Merck Index*.

On page 6 of the Office Action, the Examiner notes Applicants' arguments that the prior art is directed to bacteria which are "genetically resistant" to antibacterial agents, whereas the claims are directed to bacteria which are

"phenotypically resistant", the later which do not multiply at the time of exposure, and that these bacteria are targeted by different antibiotics. However, the Examiner contends that it is unclear how Applicants can be sure that the claimed bacteria do not multiply since, even at stationary phase, they are growing, even though their numbers are in equilibrium with those of non-growing bacteria.

In addition, the Examiner states that while Applicants argue that bacteria can possess two types of resistance, i.e., phenotypic and genetic resistance, such has not been substantiated with appropriate evidence.

For the following reasons, Applicants respectfully traverse the Examiner's rejections.

Enclosed herewith, is a copy of Hu et al (2000) that discusses the definition of "phenotypic resistance". Hu et al (2000) describes "phenotypic resistance" as being a transient state in which a non-actively growing (dormant) bacterial cell is able to tolerate a specific antibacterial agent. As soon as the cell becomes actively growing, the cell becomes susceptible to the antibacterial agent to which is was previously resistant (see pages 6358, 6360 (left column) and 6363). By contrast, "genetic resistance" is conferred by the presence of a resistance gene. Genetic resistance is only effective in actively growing (dividing) bacterial cells.

As noted above, the claims have been amended to clearly refer to non-growing, i.e., dormant cultures.

Indeed, the Examiner has noted that the application appears to be directed to testing of pathogenic bacteria that exhibit "dormancy *in vivo*".

The examples provided in the specification clearly disclose adequate methods of killing bacterial to leave only dormant (live) bacteria behind in the test sample (e.g., Example 1). The description states that dormant bacteria *in vivo* can be returned to an actively growing state by, for example, administering steroids to the host animal (page 2, line 37 to page 3, line 3).

After the dormant bacteria are induced back to the actively growing state, further doses of the original antibiotic can be administered by the methods described in the examples. Where the antibiotic is then effective in killing the previously dormant bacteria, the resistance shown during dormancy must have been of the transient, i.e., phenotypic type and not genetic.

The Examiner further notes Applicants' arguments that "genetic resistance occurs when a gene mutates and so confers resistance to a particular antibacterial agent, i.e., a permanent resistance". However, the Examiner states that this argument fails to consider the transfer of antibiotic resistance plasmids between bacteria which is not "permanent". Hence, the Examiner concludes that these arguments are not persuasive.

The Examiner is requested to note that a single bacterium possessing a genetic resistance to a particular antibacterial agent, e.g., an agent used in medicine to kill that bacterial species, can have the genetic resistance localized to a specific genetic locus, e.g., in the genomic DNA or on a plasmid. In

contrast, phenotypic resistance can not be localized to a particular genetic locus.

Throughout the life of the bacterium, a genetic locus within the genome conferring resistance will be permanent, as it provides the organism with the means to survive exposure to that particular antibacterial agent.

In the case of genetic resistance conferred by a plasmid, the organism will retain the plasmid because it provides a survival advantage over not retaining the plasmid. When the organism divides during reproduction, one of the resulting bacteria, the parent as it were, will continue to retain the plasmid. The bacterium not receiving the plasmid, since it came into existence as an individual, has never actually possessed the plasmid and has not, therefore, lost the genetic resistance. Thus, it can be seen that plasmid resistance is a permanent resistance as it is not actually lost.

The following example demonstrates the difference in permanency between genetic and phenotypic resistance:

A single organism possessing resistance to an antibacterial agent is placed in liquid nitrogen for any time period, for example, a million years. The organism is then removed from the nitrogen, thawed out and allowed to divide to produce a first generation. The first generation is then exposed to the antibacterial agent to which the original organism was resistant.

If the organism possessed a genetic resistance before freezing, then the first generation will also be resistant to the antibacterial agent.

If the organism possessed a phenotypic resistance before freezing, then the first generation will be sensitive to the antibacterial agent.

Hence, a skilled person would readily understand the different between a permanent genetic resistance and a transient phenotypic resistance (also known as tolerance).

The Examiner goes on to state that there is nothing in the cited references to require that the cells be in "exponential", rather than "stationary phase".

Applicants respectfully submit that amending the phrase "stationary phase" to "dormant" differentiates the presently claimed invention from the cited reference because each of the cited references discusses the "growth" of the bacteria of interest. The bacteria of the present invention are dormant, i.e., are not actively growing.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Sahm et al, alone or when combined with the teachings of Pelczar, George et al, Shomura et al and Barth, Murray et al and the Merck Index and in any event, the combination thereof can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejections.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration, and allowance are requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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